Lab Interpretation in a Functional Medicine Practice

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What is Functional Medicine?

- A medical practice or treatment that focuses on optimal functioning of the body and its organs, usually involving systems of holistic or alternative medicine.

- Functional Medicine helps clinicians identify and ameliorate dysfunctions in the physiology and biochemistry of the human body as a primary method of improving patient health.
The Functional Medicine Tree

Foundational lifestyle factors:
- Sleep/Relaxation
- Exercise
- Nutrition/Hydration
- Stress levels/Resilience
- Relationships/Networks
- Genetics
- Trauma
- Microorganisms
- Environmental Pollutants
These core imbalances may include:

- Neurotransmitter and hormonal imbalances
- Oxidation-reduction imbalances and mitochondriopathy
- Detoxification and biotransformational imbalances
- Immune and inflammatory imbalances
- Digestive, absorptive, and microbiologic imbalances
- Structural imbalances from cellular membrane function to the musculoskeletal system
Why run more Extensive Testing?

- As Naturopathic doctors, the patients we see have:
  - Often been sick a long time
  - Often have seen multiple physicians already
  - Have often traveled to see specialists, sometimes in other countries, certainly in other states.
  - Have likely seen multiple alternative health practitioners
  - Have likely already spent thousands of dollars on medications, and/or supplements.
  - They are looking for the root cause of their health concerns – and alternative testing can often yield answers to redirect treatment and provide hope for the patient.
The Tests

THYROID HORMONE ASSESSMENT, SALIVARY CORTISOL AND SEX HORMONE TESTING, URINARY NEUROTRANSMITTER ASSESSMENT, COMPREHENSIVE DIGESTIVE STOOL ANALYSIS
Thyroid Assessment
TSH, TT4, FT4, FT3, ANTI-TPO, FERRITIN, D3
Testing Considerations when a Patient presents with Hypothyroid Symptoms

These include:

- Autoimmune reactions affecting thyroid gland
- Lack of production from gland (T4)
- Poor conversion of T4 to T3
- Decreased absorption of T3 into the cells
- Decreased intracellular transport of T3
- Suboptimal thyroid receptor function
Initial Basic Functional Thyroid Testing

- TT4, fT4, fT3, TSH, TPO, Vitamin D3, Ferritin
- Basal Body Temperature
Basal Body Temperature

- A low basal body temperature (BBT) = less than 97.6F averaged over a minimum of 3 days.
Interpretation of Test Results

- Production of thyroid hormone is best measured with Total T4.
- If lower than normal consider:
  - Low substrates for T4
    - Iodine and Tyrosine are main substrates
  - Pituitary hypofunction
    - Acute or chronic stress raises CRH and cortisol, both of which suppress TSH and lower production of thyroid hormones
  - Poor nutrition
  - Thyroid gland destruction
Factors that Affect Thyroid Function

Factors that contribute to proper production of thyroid hormones
- Nutrients: iron, iodine, tyrosine, zinc, selenium vitamin E, B2, B3, B6, C, D

Factors that increase conversion of T4 to RT3
- Stress
- Trauma
- Low-calorie diet
- Inflammation (cytokines, etc.)
- Toxins
- Infections
- Liver/kidney dysfunction
- Certain medications

Factors that inhibit proper production of thyroid hormones
- Stress
- Infection, trauma, radiation, medications
- Fluoride (antagonist to iodine)
- Toxins: pesticides, mercury, cadmium, lead
- Autoimmune disease: Celiac

Factors that increase conversion of T4 to T3
- Selenium
- Zinc

RT3 and T3 compete for binding sites

Factors that improve cellular sensitivity to thyroid hormones
- Vitamin A
- Exercise
- Zinc
Interpretation of Test Results

- Comparison of fT4 and TT4 provides assessment of binding (TBG)
- If fT4 is lower within its normal range relative to where TT4 is within its normal range, this would indicate greater than normal binding.
- Excessive binding can be caused by any excessive estrogen state but most commonly by oral estrogen therapy or excessive thyroid replacement therapy as well as sleep deprivation.
Thyroid Gradient Levels, Example 1
Comparison of fT3 and fT4 provides interpretation of conversion of T4 to the active form of T3.

Additionally, comparing fT3 to rT3 also provides information as to how T4 is being converted.

- fT3 and rT3 are normally produced in approximately equal amounts from T4.
- If rT3 is higher, within it’s range relative to fT3, fT3 is being favored
  - rT3 blocks some of the action of already lower than ideal fT3.
Autoimmune reactions are the number one cause of all thyroid disorders.

Thyroid peroxidase antibody testing will reveal a thyroid autoimmune reaction 90% of the time.

When anti-TPO are elevated, it is difficult to assess at what state the autoimmune reaction and attack is occurring.

High serum antibodies are found in active phase chronic autoimmune thyroiditis. Thus, an antibody titer can be used to assess disease activity in patients that have developed such antibodies.
Approaches to Autoimmune Thyroid Disease

- Eliminate the agent/agents initiating the inflammatory response
  - Inflammatory foods
  - Inflammatory lifestyle habits
- Reduce gut inflammation and restore normal GI flora
- Supplementations
  - Selenium - In the event of selenium deficiency, glutathione peroxidase cannot thyroid cells from the H2O2 produced in thyroid hormone production and damage to the cells can result.
    - Curcumin, Resveratrol
  - Retest levels of anti-TPO 60-90 days out.
Vitamin D3 is necessary for optimal thyroid receptor function.

- Vitamin D3 should be 60-80ng/mL for optimal thyroid receptor function

Ferritin affects thyroid intracellular transport and utilization.

- Ideally 90-100ng/mL for optimal thyroid hormone transport and utilization
Salivary Adrenal and Sex Hormone Testing

CORTISOL X 4, ESTRADIOL, ESTRIOL, PROGESTERONE
HPA Axis

- The hypothalamic pituitary adrenal (HPA) axis is our central stress response system.
- The HPA axis is a dynamic intertwining of the central nervous system and endocrine system.
External stressors → biochemical signals
  - many of which influence the feedback loops of the HPA axis.

- Influences hormones, cytokines, glucose regulation, and other metabolic processes.
- When optimally functioning, plays a critical role in the overall health of our patients.
Normal exposure to cortisol
- Tissues experience fleeting glimpses of the alarm catecholamines and cortisol.

Prolonged exposure to cortisol
- may continually activate the HPA axis and affect the balance of hormone and cell mediators.

Frequent release of cortisol due to chronic stress affects the hypothalamic and pituitary feedback loops
- may lead to persistent activation and depletion of the system.
Why are we investigating adrenal function in our patients?

Because our patients are STRESSED.

The American Institute of Stress reports that 75–90 percent of visits to primary care physicians are stress-related; therefore, supporting HPA axis homeostasis is a significant clinical goal for a broad range of patients.
Gray Area between Adrenal Insufficiency and Hypercortisolism

- In a seminal paper published in 1950 in the British Medical Journal, Hans Selye MD, PhD, described the human physiological response to prolonged stress as a General Adaptation Syndrome (GAS).

- Selye identified the three stages—alarm, resistance, and exhaustion.

- With the stages of resistance and exhaustion, we find suboptimal adrenal function or hypoadrenia accompanied by a variety of symptoms.

Common Effects of Stress

On the Body
Headache
Muscle tension or pain
Chest pain
Fatigue
Change in sex drive
Stomach upset
Sleep problems
Weight gain

On the Mood
Anxiety
Restlessness
Lack of motivation or focus
Feeling overwhelmed
Irritability or anger
Sadness or depression

On behavior
Overeating or undereating
Angry outbursts
Drug or alcohol abuse
Tobacco use
Social withdrawal
Exercising less often

www.mayoclinic.org
Suboptimal Diurnal Rhythm
Figure 1. Circadian Cortisol Profile

Free Cortisol (nM)

8 AM Noon 4 PM Midnight

Reference Ranges

Patient Results
Assessment of potential Adrenal Dysfunction

- Saliva testing is proving to be the most reliable medium for measuring hormone levels.
- Saliva measures the free, bioavailable hormone levels in the body, unlike serum which represents total hormone levels (free and bound).
- Clinically, it is far more relevant to test the amount of hormones delivered to the tissue receptors as this is a reflection of the active hormone levels of the body.
Salivary Testing Reveals Bioavailable hormone

- When blood is filtered through the salivary glands, the bound hormone components are too large to pass through the cell membranes of the salivary glands.
- Only the unbound hormones pass through and into the saliva.
- What is measured in the saliva is considered the “free”, or bioavailable hormone, that which will be delivered to the receptors in the tissues of the body.
Salivary Sex Hormone Testing

- Estradiol
- Estriol
- Progesterone

- DHEA and Testosterone can be accurately tested in serum if lab has ranges for the different age group for females, which not all have. Saliva testing is a choice if insurance coverage is not available as it is an affordable method of testing for patients.

- SHBG measurement is a consideration as well.
When to test for Salivary Sex Hormones

- When clinical presentation suggests hormone imbalance
- Baseline levels should be measured for any patient considering hormone restoration therapy.
- Follow-up testing is typically done 3-4 months after initiation of therapy
- Pre-menopausal or peri-menopausal women should test on days 18-21 of their cycle.
- 4 point testing allows for a more accurate idea of average production throughout a 24 hour period.
<table>
<thead>
<tr>
<th>Saliva Hormone Test</th>
<th>Result</th>
<th>Units</th>
<th>L</th>
<th>WR</th>
<th>H</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrone (E1)*</td>
<td>2.60</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>1.0-10.8 pre menopausal (1.5-10.8 supplementation)</td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>2.60</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>1.0-10.8 pre menopausal (1.5-10.8 supplementation)</td>
</tr>
<tr>
<td>Estriol (E3)*</td>
<td>19.04</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>6.1-49.0 female (30.0-60.0 supplementation)</td>
</tr>
<tr>
<td>EQ (E3 / (E1 + E2))</td>
<td>32.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200-600 pre; post with supplementation</td>
</tr>
<tr>
<td>Progesterone (Pg)</td>
<td>84.64</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>127.0-446.0 pre menopausal (luteal) (500-3000 supplementation)</td>
</tr>
<tr>
<td>Ratio of Pg/E2**</td>
<td>32.55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>200-600 pre; post with supplementation</td>
</tr>
<tr>
<td>Testosterone*</td>
<td>19.04</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>6.1-49.0 female (30.0-60.0 supplementation)</td>
</tr>
</tbody>
</table>

### Adrenals

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Result</th>
<th>Units</th>
<th>L</th>
<th>WR</th>
<th>H</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHEA*</td>
<td>111.08</td>
<td>pg/ml</td>
<td></td>
<td></td>
<td></td>
<td>106.0-300.0 female</td>
</tr>
<tr>
<td>Cortisol Morning</td>
<td>4.92</td>
<td>nmol/L</td>
<td></td>
<td></td>
<td></td>
<td>5.1-40.2; optimal range: 18-35†</td>
</tr>
<tr>
<td>Cortisol Noon</td>
<td>2.08</td>
<td>nmol/L</td>
<td></td>
<td></td>
<td></td>
<td>2.1-15.7; optimal range: 6-12†</td>
</tr>
<tr>
<td>Cortisol Evening</td>
<td>1.05</td>
<td>nmol/L</td>
<td></td>
<td></td>
<td></td>
<td>1.8-12; optimal range: 4-8†</td>
</tr>
<tr>
<td>Cortisol Night</td>
<td>0.41</td>
<td>nmol/L</td>
<td></td>
<td></td>
<td></td>
<td>0.9-9.2; optimal range: 2-6†</td>
</tr>
</tbody>
</table>

### Hormone Comments:

- Progesterone to estradiol (Pg/E2) ratio and reported symptoms are consistent with progesterone insufficiency (estrogen dominance). Supplementation with topical progesterone to correct this deficiency is a consideration. Note: The progesterone level is suggestive of an anovulatory cycle, luteal phase failure or collection outside of luteal phase. Patient reports salivary collection on day 21 of cycle.
- Suboptimal testosterone may relate to increased risk of osteoporosis, low libido, vaginal dryness and heart disease.
- Diurnal cortisol pattern and reported symptoms are consistent with established (Phase 3) HPA axis (adrenal gland) dysfunction, although concomitant thyroid and/or iodine insufficiency cannot be ruled out.

### Notes:

L = Low (below range)  WR = Within Range (within range)  H = High (above range)

*This test was developed and its performance characteristics determined by Labrix Clinical Services, Inc. The US FDA has not
Benefits to Salivary Testing

- Convenient for patient to do at home
- No variability in cortisol level based on venipuncture induced stress
- Affordable
- 4 readings over 24 hours allows for investigation of diurnal cortisol rhythm.
- 4 readings in 24 hours allows for average sex hormone levels throughout day and night.
Pooled Tube Provides More Accurate Sex Hormone Levels

- Sex hormone levels fluctuate throughout the day as well as throughout the month while other hormones, like cortisol, have a predictable diurnal rhythm.

- As a result, many lab measurements will give falsely elevated or depressed values if only evaluating one sampling for sex hormones.
Urinary Neurotransmitters
Validity of Urinary Neurotransmitter Testing

Proven to be clinically relevant in treating neurotransmitter imbalance symptoms, such as:
- Depression, anxiety, low energy, insomnia, ADD, OCD, addiction, and chronic pain.

Preformed and studied in the US for 20+ years.
Method: Liquid chromatography & mass spectrometry.
Why choose Urinary NT Testing?

- Assess for imbalances between the various neurotransmitters that are likely playing a role in:
  - Anxiety
  - Depression
  - Insomnia
  - ADHD

- Allows for guided decision making regarding medication and/or supplement choices:
  - For Targeted amino acid therapy, will allow up to better select which pathway needs more attention
Limitations?

- We are not able to test solely neurotransmitters being secreted in the brain.
- Neurotransmitters are secreted all through the body, in neurons of both the central and peripheral nervous systems.
  - 80-90% of serotonin is secreted in GI tract
  - Epi and Norepi are secreted in the periphery as part of the stress response
- Neurotransmitter receptors are found in all tissues, not just nervous tissues.
  - Dopamine receptors in coronary, renal and cerebral tissues
  - Glutamate receptors identified in the heart, lungs and endocrine glands
- Therefore, while we are not testing what is in the brain or in the synapse, we are getting a good indication of whole body levels of neurotransmitters.
## Urinary Neurotransmitter Testing

<table>
<thead>
<tr>
<th>Neurotransmitter Test</th>
<th>Result</th>
<th>Units</th>
<th>L</th>
<th>WR</th>
<th>H</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin</td>
<td>65.10</td>
<td>μg/gCr</td>
<td></td>
<td></td>
<td></td>
<td>74.13 - 111.19</td>
</tr>
<tr>
<td>GABA</td>
<td>2.25</td>
<td>μMol/gCr</td>
<td></td>
<td></td>
<td></td>
<td>2.76 - 4.14</td>
</tr>
<tr>
<td>Dopamine</td>
<td>140.83</td>
<td>μg/gCr</td>
<td></td>
<td></td>
<td></td>
<td>139.1 - 208.7</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>21.27</td>
<td>μg/gCr</td>
<td></td>
<td></td>
<td></td>
<td>28.07 - 42.11</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>3.49</td>
<td>μg/gCr</td>
<td></td>
<td></td>
<td></td>
<td>3.36 - 5.05</td>
</tr>
<tr>
<td>Glutamate</td>
<td>80.56</td>
<td>μMol/gCr</td>
<td></td>
<td></td>
<td></td>
<td>60.69 - 91.03</td>
</tr>
<tr>
<td>N/E Ratio</td>
<td>6.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;10.0</td>
</tr>
<tr>
<td>Creatinine</td>
<td>101.54</td>
<td>mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific Gravity</td>
<td>1.013</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
When to consider urinary NT testing

- When a pronounced mood complaint is part of a patient’s treatment request including cognitive and mood concerns, stress, insomnia and fatigue, decreased motivation, cravings and addictions, and/or pain issues.

- If you have been working with a patient and his/her hormones are beautifully balanced, but s/he is still experiencing symptoms.
Comprehensive Digestive Stool Analysis
When to Order

- Digestive stool analysis offers a user-friendly way to provide clinicians with valuable insight into GI imbalances.
- Provides actionable clinical information for patients presenting with GI complaints.
- Aids clinicians in the identification of root cause(s) of digestive discomfort and supports identification of targeted treatments.
Comprehensive Digestive Stool Analysis

- Can help assess
  - digestive and absorptive functions
  - presence of opportunistic pathogens
  - efficacy of therapeutic remediation of GI disorders.

- Antimicrobial susceptibility testing to prescriptive and natural agents can be performed for appropriate bacterial and fungal species.
CDSA Components

Stool analysis evaluates:
- Digestion/Absorption Markers
- Gut Metabolic Markers
- Gut Microbiology Markers
- Gold standard O&P (ova & parasite) technology as well as EIA (Enzyme Immunoassay) for identification of common parasites

Offers insight into:
- Maldigestion
- Malabsorption
- Irritable Bowel Syndrome (IBS)
- Altered GI immune function
- Bacterial/fungal overgrowth
- Chronic dysbiosis
Digestion Markers

- Chymotrypsin
- Pancreatic Elastase 1
- Putrifactive Short-Chain Fatty Acids
- Meat Fibers/Vegetables Fibers
Absorption Markers

- Triglycerides
- Long Chain Fatty Acids
- Cholesterol
- Cholesterol
- Phospholipids
- Fecal Fat
Metabolic Markers

- Short Chain Fatty Acids
- SCFA Distribution
- N-Butyrate
- pH
- Beta-glucuronides
Immunology Markers

- Eosinophil Protein X
- Calprotectin
Eosinophil Protein X

- Detects inflammation and tissue damage in GI tract
- May be elevated in:
  - Food allergy
  - Protein sensitive enteropathy
  - Helminthic infection
  - IBD
  - Allergic colitis
  - GERD
Calprotectin

- **A marker to help us differentiate between IBS and IBD**
- Highly-sensitive clinical biomarker for GI-specific inflammation.
- Belongs to a group of calcium-binding neutrophil-derived proteins. Calprotectin makes up 60% of the cytosolic proteins within the neutrophil.
- It is very resistant to bacterial degradation in the gut and is stable in stool for up to one week at room temperature.
- Calprotectin is the noninvasive "test of choice" for quantifying the degree of GI inflammation and differentiating Irritable Bowel Syndrome (IBS) from Inflammatory Bowel Disease (IBD).
Calprotectin

**Distinguishing**
Distinguishing between patients with Irritable Bowel Syndrome (IBS) and Inflammatory Bowel Disease (IBD) with a 99% Positive Predictive Value

**Assisting**
Assisting in the selection of patients with abdominal symptoms who may require further diagnostic procedures

**Selecting**
Selecting patients for endoscopy as well as monitoring the response to treatment.
Microbiology Investigation Includes

- H. pylori stool antigen
- Shigella
- Campylobacter
- Clostridium
### Microbiology Profile, stool

<table>
<thead>
<tr>
<th>BACTERIOLOGY CULTURE</th>
<th>Expected/Beneficial flora</th>
<th>Commensal (Imbalanced) flora</th>
<th>Dysbiotic flora</th>
</tr>
</thead>
<tbody>
<tr>
<td>NG Bacteroides fragilis group</td>
<td>4+ Bifidobacterium spp.</td>
<td>2+ Enterobacter cloacae</td>
<td>4+ Klebsiella oxytoca</td>
</tr>
<tr>
<td>4+ Escherichia coli</td>
<td>3+ Lactobacillus spp.</td>
<td>3+ Gamma hemolytic strep</td>
<td></td>
</tr>
<tr>
<td>1+ Enterococcus spp.</td>
<td>1+ Clostridium spp.</td>
<td>1+ Staphylococcus aureus</td>
<td></td>
</tr>
<tr>
<td>NG = No Growth</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Stool Microbiology
### Microbial Factors in the AI Disease

<table>
<thead>
<tr>
<th>Proteus mirabilis</th>
<th>Klebsiella pneumoniae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysins</td>
<td>Nitrogenases</td>
</tr>
<tr>
<td>Ureases</td>
<td>Pulullanases</td>
</tr>
<tr>
<td>GLU-SER-ARG-ARG-ALA-LEU</td>
<td>GLN-THR-ASP-ARG-GLU-ASP</td>
</tr>
<tr>
<td>ESRRAL</td>
<td>QTDRED</td>
</tr>
<tr>
<td>ISO-ARG-ARG-GLU-THR</td>
<td>ASP-ARG-ASP-GLU-ASP</td>
</tr>
<tr>
<td>IRRET</td>
<td>DRED</td>
</tr>
<tr>
<td>GLU-GLN-ARG-ARG-ALAALA</td>
<td>GLN-THR-ASP-ARG-GLU-ASP</td>
</tr>
<tr>
<td>EQRRAA</td>
<td>QTDRED</td>
</tr>
<tr>
<td>LRRRI</td>
<td>DRED</td>
</tr>
<tr>
<td>LEU-ARG-ARG-GLU-ISO</td>
<td>ASP-ARG-GLU-ASP</td>
</tr>
<tr>
<td>Gly-x-Pro</td>
<td>GxP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Self-antigens</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-DR4/1</td>
</tr>
<tr>
<td>Collagen XI</td>
</tr>
<tr>
<td>HLA-B27</td>
</tr>
<tr>
<td>Collagens I, III, and IV</td>
</tr>
</tbody>
</table>

Autoimmunity in Rheumatic Diseases Is Induced by Microbial Infections via Cross reactivity or Molecular Mimicry, Autoimmune Diseases, Volume 2012 (2012)
“Functional medicine is about causes, not symptoms. It is getting to the root of the problem.”
—Mark Hyman, MD
Thank You!

Dr. Laura Jones
Whole Health Concord
Concord, NH
www.NaturalMedicineNH.com